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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, DEEPAK R	
ART UNIT	PAPER NUMBER
1624	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/336,266	Applicant(s) Bemis et al.
	Examiner Deepak Rao	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 5, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *4-12, 15, 24-38, 46-48, and 62-67* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *4-12, 15, 24, 25, 38, 46-48, 62, 64, and 66* is/are allowed.

6) ☒ Claim(s) *26, 28, 30-37, 63, 65, and 67* is/are rejected.

7) ☒ Claim(s) *27 and 29* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This office action is in response to the amendment filed on September 5, 2002.

Claims 38, 4-12, 15, 24-37, 46-48 and 62-67 are pending in this application.

The following rejections are withdrawn:

The rejections under 35 U.S.C. 112, second paragraph of the previous office action are withdrawn in view of the amendments.

The following rejections are maintained:

Claims 26, 28, 30-37, 63, 65 and 67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of inflammatory diseases such as rheumatoid arthritis, bone destructive diseases, does not reasonably provide enablement for treating infectious diseases, proliferative diseases, neurodegenerative diseases, viral diseases, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. The reasons of the previous office action are incorporated here by reference.

Applicant first submits that "proliferative diseases" and "viral diseases" have been deleted from claims 26, 63, 65 and 67 and dependent claims 30 and 32 have been canceled. However, there was no instruction to cancel claims 30 and 32 in the amendment and these claims are still pending and are rejected for the same reasons provided in the previous office action.

Next, applicant argues that "the diversity of actions of p38 kinases gives rise to a broad range of applications for the p38 inhibitors of the present invention". Applicant further relies on documents (attached as Exhibits 2-10) to establish a link between p38 and inflammatory, autoimmune, infectious diseases. However, many of the documents are not state of the art references at time the application was filed. Further, they do not show any support to establish the link for many of the diseases recited in the claims. Each of the submitted references is discussed in detail below:

Applicant relies on Suzuki (2000) and argues that according to Suzuki, "p38 inhibitors may be effective for the treatment of rheumatoid arthritis and other inflammatory and autoimmune diseases in which inflammatory cytokines play a crucial role". First the reference is not a publication of at the time the application was filed. See MPEP § 2164.05(a) wherein it is provided that: "The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); *In re Budnick*, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976)". Further, the reference is specific to the involvement of p38 MAP kinase inhibitors in the pathophysiology of rheumatoid arthritis. The reference does not provide "a link" between p38 inhibitors and all the other diverse diseases recited in the instant claims. Even with respect to its action against the production of inflammatory cytokines, the reference

provides that "the mechanism of its action is still controversial" (see page 26, col. 2), thus, confirming the unpredictability of the activity of the claimed inhibitors.

Applicant further cites Badger I (1996) and argues that the reference "reports the efficacy of a p38 inhibitor in a variety of TNF-α mediated animal models of inflammatory diseases that arise by both autoimmune and infectious pathways". First, the reference discussion is pertinent to pyridinyl imidazole compounds (see page 1454). Further, the reference clearly outlines regarding the dual activity of the compounds that "these compounds do not have overt immunosuppressive activity" (see page 1460, col. 2) and confirms only with respect to rheumatoid arthritis (RA), "it is safe to assume that *in vivo*, the compound may induce its antiarthritic activity" and does not provide "a link" between p38 inhibitors and autoimmune diseases in general.

Badger II (2000) also discussing pyridinyl imidazole class of compounds, concludes that the "inhibitors could provide significant benefit in the treatment of chronic inflammatory diseases such as RA" (see page 182, col. 2), however, clearly expresses the uncertainty with respect to blocking of other cytokines "at present, comprehensive mechanisms detailing all of the steps involved in cytokine regulation are unknown" (see page 181, col. 2).

Hommes (2002), specifically addresses the role of MAPK inhibitors in a chronic inflammatory disease, Crohn's Disease (see the concluding statement "we propose that such a therapy may constitute a promising novel avenue for the treatment of CD"), however, the

reference does not generalize the use of the inhibitors for the treatment of the various diseases of the instant claims.

Ballard-Croft (2001) provides that "While p38 MAPK plays a role in regulating inflammatory cytokine production as well as many other cellular responses to stress, the biological consequences of MAPK activation in the heart are diverse and not clearly understood" (see page H1970, col. 2) and further "... the down stream substrates for this kinase group within the heart remain undefined" (see H1979, col. 2). Therefore, the reference does not provide conclusive evidence that p38 inhibitors generally provide therapeutic benefit in the diverse list of diseases of the instant claims.

Shimamoto (no publication date provided) provides that the p38 MAPK inhibitor activity in cardiac hypertrophy and congestive heart failure, however, the reference does not provide any generalized use of the inhibitors in the assorted disease states recited in the instant claims.

Nick (2000) based on studies focused on the function of p38 MAPK inhibitors "suggests the potential for selective analysis and modulation of neutrophil influx in pulmonary inflammation" (see page 2159, col. 1), however, clearly states that "The effects of systemic p38 MAPK inhibition on pulmonary inflammation has not been described" (see page 2158, col. 2).

Legos (2001) first provides that 'activation of the p38 MAPK pathway has been implicated in playing a role in the regulation of pro-inflammatory cytokines' (see page 70, col. 2), however, concludes that "detailed in vitro studies are necessary to fully understand the role of p38 following ischemia and the mechanism(s) by which it can be beneficial".

Barancik (2000) only provides "the detrimental effect of p38-MAPK activation during ischemia", however, there is no generalized discussion with regards to the role of the inhibitors as therapeutic agents in the treatment of the diverse diseases of the instant claims.

Applicant did not provide any argument in support for the recitation of the terms "neurodegnerative diseases", "infectious diseases", etc. that were specifically addressed in the previous office action. Further, the claim includes 'angiogenic disorders, organ hypoxia, vascular hyperplasia' for which no evidence has been offered to support the nexus between p38 inhibition and treatment related to the diseases. 'Angiogenesis' is the process of vascularization of a tissue involving the development of new capillary blood vessels and therefore, is not seen as being a disease or disorder, but as an absolutely essential body process. Thus, there is no enablement for treating something which is not itself a problem and is indeed essential for life. Further, no supporting evidence for the enablement of "thrombin-induced platelet aggregation or conditions associated with prostaglandin endoperoxide synthase-2" is provided.

Therefore, based on the reasons stated above, most of the references are not state of the art references as of the filing date of the application; most discuss a narrow group of p38 MAPK inhibitors and do not provide any data or activity related to all types of p38 inhibitors in general such that a skilled artisan could extrapolate to the use of the compounds in the treatment of the various diseases of the claims. In view of the above, it is maintained that the specification is enabling for the use of the compounds in treatment of "inflammatory diseases, destructive bond disorders, reperfusion/ischemia in stroke, myocardial ischemia, renal ischemia and cardiac

hypertrophy" (as claimed in claims 26, 63, 65 and 67); "rheumatoid arthritis, Chron's disease" (claim 28) and does not enable the treatment of the other diseases recited in the claims.

The following rejections are necessitated by the amendment:

Claims 30 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. Claim 30 recites the limitation "said method is used to treat a proliferative disease" in line 2. There is insufficient antecedent basis for this limitation in claim 26 on which the claim is dependent.
2. Claim 32 recites the limitation "said method is used to treat a viral disease" in line 2. There is insufficient antecedent basis for this limitation in claim 26 on which the claim is dependent.

Allowable Subject Matter

Claims 38, 4-12, 15, 24-25, 46-48, 62, 64 and 66 are allowed.

Claims 27 and 29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Deepak Rao
Primary Examiner
Art Unit 1624

September 17, 2002